PATENT
Atty. Docket No.: 401-UTL-0 (18528.010)

REMARKS

Claims 1, 8 and 33-73 are currently pending. Claims 2-7 and 9-32 were previously canceled without prejudice or disclaimer. Please cancel claims 1, 8, 34-42, 48-50 and 52-53 without prejudice. Applicants reserve the right to prosecute claims of similar or differing scope. New claims 64-73 have been added. Support for these claims can be found throughout the specification. For example, support for a PYY agonist analog that is a peptide which does not comprise YP as its first two consecutive N-terminal amino acids, and which elicits a pharmacological effect at a Y2, Y5 or Y7 receptor greater than that of PYY[1-36] at a Y1 receptor can be found at least on page 2, lines 12-14; page 3, lines 15-25; page 4, lines 8-19; page 6, lines 4-11 and 14-19; page 15, lines 5-6; in Table 1, pages 10-11; and in Examples 1 and 2 of the specification as filed. Support for claim 70 can be found at least on page 4, lines 22-27; on page 6, lines 20-25 and on page 7, lines 10-12. Support for claim 72 can be found at least on page 21, lines 10-12. Support for claim 73 can be found at least on page 5, line 30 and in Table 1. Support for the amendment of claim 51 is found at least on page 7, lines 23-28. Upon entry of the present amendment, claims 33, 43-47, 51 and 54-73 will be pending. No new matter has been introduced by way of these amendments.

Amendment to the Specification

Applicants note that a patent cited in the first paragraph of the detailed description on page 9 of the specification contains an obvious typographical error in the patent number. This paragraph includes description of prior art directed to the use of PYY receptor agonists to increase weight gain. U.S. Patent No. 6,315,203 is directed to an auto barcode reader. The correct citation should be to U.S. Patent No. 6,316,203. Applicants respectfully request correction of this simple typographical error.

Interview Summary

Applicants respectfully submit the following summary of the substance of the interview.

NPY_{3-36}, PP and Ac-PYY[22-36]. Additionally, the application points to several published references and patents as sources of other PYY agonists, and these have been incorporated by reference. Where information is incorporated by reference to patents or patent applications in the text of the specification, "(t)he information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed." (M.P.E.P. 2163.07(b)). Furthermore, a patent application "need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986); MPEP §601. In addition to knowing what is in the art, the skilled artisan has been specifically directed to known PYY agonists.

Such examples of Y receptor agonists incorporated by reference include selective Y1 receptor agonists Pro^{34}-NPY and Pro^{34}-PYY, as well as the Y2 receptor agonist NPY_{13-36} (see pages 8-9 of Gehlert, D. R., Proc. Soc. Exp. Biol. Med. 218:7-22 (1998); Gehlert is cited in Table 1 of the specification). The Yoshinaga reference, cited on page 2, lines 14-15 of the specification, lists many Y receptor agonists, including PYY(4-36), PYY(6-36), PYY(10-36) and PYY (13-36), to name but a few. Yoshinaga also reports that PYY (22-36) was more potent than amino terminal fragments of PYY in gastric acid and endocrine pancreatic secretion analyses, and further cites a report by Whalestedt et al., concluding that PYY (13-36) was as effective as PYY (1-36) in suppressing norepinephrine release from the rat vas deferens (Yoshinaga reference, page G699 left column). US Patent 6,316,203, cited on page 9 of the application discusses the rank order of potency of PYY, NPY, [Leu^{31}, Pro^{34}]NPY, NPY_{2-36} and NPY_{13-36} agonists at the Y5 receptor (see column 1). US Patent Nos. 5,604,203 and 5,696,093, are cited on page 19, lines 6-8 of the specification; the former discloses Y receptor agonists having antisecretory effects, and the latter reports a Y2 receptor agonist with low affinity for the Y1 receptor and no pressor activity (see column 2 of US Patent 5,696,093).

Although many PYY agonist analogs are known in the art and incorporated by reference into the specification, Applicants have further attempted to accommodate the Examiner by amending the claims to recite only those PYY agonist analogs which bind a subset of Y-receptors to elicit a specific subset of pharmacological responses (i.e., reduction of food intake, appetite, nutrient availability, caloric efficiency, or body weight

PATENT
Atty. Docket No.: 401-UTL-0 (18528.010)

On May 9, 2006, the Examiner in the above captioned application together with Supervisory Patent Examiner Gary Nickol, conducted an in-person interview with Applicant's representatives, David Marsh, James Butler, Richard Pitter, and Susan Fitch. At the interview, Applicants' representatives appreciated the opportunity to discuss the outstanding rejections under 35 U.S.C. §§ 102(b) and 103(a) based on the Yoshinaga and Okada references, as well as the enablement and written description rejections under 35 U.S.C. § 112, First Paragraph. It was agreed that the Applicants would submit a supplemental response by the end of the following week.

Withdrawn Objections and/or Rejections

Applicants note, with appreciation, the Examiner's acknowledgment in the Office Action mailed November 23, 2005 that the Morley reference neither teaches nor suggests a reduction in food intake upon treatment with PYY, and that the rejection of claims 1, 33, 38, 42, 48-50 and 52-54 under 35 U.S.C. 102(b) as being anticipated by Morley has been withdrawn.

Applicants also note with appreciation that the rejection of claim 51 under 35 U.S.C. 103(a) as being unpatentable over Morley in view of Naslund has been withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph – Enablement

In the Office Action mailed November 23, 2005, claims 1, 8, 33-46 and 48-63 were rejected under 35 U.S.C. § 112, first paragraph. The Examiner alleges that the specification does not reasonably provide enablement for the claimed invention commensurate in scope with the claims. Applicants respectfully disagree with this rejection to the extent it is maintained in light of the amended claims.

Although Applicants previously amended the claims to recite "wherein the PYY agonist is a peptide," the Examiner states that "the specification merely discloses two compounds: PYY and PYY (3-36), and fails to provide the characteristic structure that is critical for the function of PYY and fails to provide sufficient guidance to make such PYY agonists" (page 4 of the November 23, 2005 Office Action). This is incorrect. The specification lists several additional agonists of Y receptors in Table 1, including NPY,

gain). Methods for measuring the effects of PYY agonist analogs on food intake, gastric and gallbladder emptying, and caloric efficiency, for example, are provided in the application and can be used in the methods of the present invention to determine whether a PYY agonist analog elicits pharmacological effects. Applicants have also amended the claims to include a structural limitation, such that the PYY agonist is a peptide analog of PYY which does not comprise YP as its first two consecutive N-terminal amino acids. Support for this structural limitation is found, at least, on page 2, lines 12-14; page 6, lines 8-19 and page 12, lines 1-6 (for example, SEQ ID NO: 3, which does not comprise YP as its first two consecutive N-terminal amino acids). Methods of chemically synthesizing or recombinantly expressing peptide agonists are provided in the specification (see page 12, lines 11-29). Thus, one of ordinary skill would be able to make and use the claimed PYY agonist analogs; the invention is enabled. Applicants respectfully request reconsideration and withdrawal of the rejection of these claims for lack of enablement.

Rejections Under 35 U.S.C. § 112, First Paragraph – Written Description

Claims 1, 8, 33-46 and 48-63 were rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking written description. The Examiner states that "in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the genus of PYY agonists and the genus of agonists of a GLP-1, an exendin, and an amylin." (Office Action, 23 November 2005, pages 7-8). Applicants respectfully disagree with this rejection to the extent it is maintained in light of the amended claims.

As detailed above, PYY agonists are adequately described in the specification, and several were known in the art at the time of filing and were incorporated by reference. Similarly, description is provided for the administration of a PYY or PYY agonist with a GLP-1, an exendin, an amylin, a leptin, their agonists, or any combination thereof, as provided in claim 51. GLP-1 and GLP-1 agonists, exendin and exendin agonists, amylin and amylin agonists, leptin and leptin agonists were also known in the art, and were incorporated by reference to several patents and publications (see, at least, page 7, line 23 through page 8, line 4 of the specification).

Nonetheless, without acquiescence to the rejection and solely to advance prosecution, Applicants have further defined the genus of PYY agonists to include those PYY agonists which are peptide analogs of PYY that do not comprise YP in the first two amino acid positions, and which elicit a pharmacological effect at a Y2, Y5 or Y7 receptor greater than that of PYY[1-36] at a Y1 receptor. The amendments to the claims are fully supported by the specification. Applicants have provided sufficient structural description of the genus of PYY agonist analogs, including disclosure of additional distinguishing identifying characteristics of PYY agonist analogs, and the rejection is believed to be overcome. The skilled artisan would readily recognize that the Applicants were in possession of the claimed invention. Applicants, therefore, respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 U.S.C. § 112, Second Paragraph – Indefiniteness

Claims 1, 8, 34-41 and 52-54 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, with respect to the phrases "desirous of" and "in need thereof," the Examiner alleges that "[i]t is unclear how such a limitation, which represents a mental process, limits the subject recited in the claims" (Office Action, 23 November 2005, page 10). The Examiner further states that "[i]t is unclear how a person of skill in the art could determine whether a mouse wishes or desires to be treated with PYY or a PYY agonist" (Office Action, 23 November 2005, page 11). Applicants respectfully disagree with this rejection to the extent it is maintained in light of the amended claims.

The proper test for indefiniteness is whether every claim term, read in view of the specification, would allow a person of ordinary skill in the art to understand what is claimed. With respect to claims 56-58, Applicants submit that one of ordinary skill in the art can determine a subject population in need; the courts have held that the phrase "in need thereof" is meaningful, and that "the claims' recitation of a patient or a human 'in need' gives life and meaning to the preambles' statement of purpose." (*Jansen v. Rexall Sundown, Inc.*, 342 F.3d at 1333). Nonetheless, without acquiescence to the rejection and solely to advance prosecution, Applicants have canceled claims 1, 8, 34-42, 48-50 and

52-53, claiming a subject "desirous of," thereby rendering the rejection of these claims moot. Claim 55 has been further amended to recite a human subject who desires to reduce food intake. Support for new claims 65-70 referring to a subject population having "a condition or disorder" is found at least on page 4, line 22 through page 5, line 5 and on page 6, line 20 through page 7, line 12. Thus, the subject population is particularly pointed out and distinctly claimed. Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

Rejections Under 35 U.S.C. § 102(b)

Claims 1, 8, 33-42, 47-49 and 52-60 and 62 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Yoshinaga, et al., (*Am. J. Physiol.* 263:G695-701, 1992). The Examiner alleges that "the intended uses and properties of the PYY or PYY agonist recited in the claims are inherent to the method taught by Yoshinaga, et al." (Office Action 23 November 2005, page 12). Applicants respectfully traverse the rejection to the extent it is maintained in light of the amended claims, because Yoshinaga does not teach, expressly or inherently, each element recited in the claims.

Yoshinaga teaches that administration of PYY and PYY(3-36) to dogs inhibits pancreatic exocrine and gastric acid secretion. Yoshinaga does not teach or suggest reducing food intake, nutrient availability, caloric efficiency or appetite, nor reducing weight, weight gain or increasing weight loss. Furthermore, Yoshinaga does not teach the claimed subject populations, i.e., human subjects, subjects in need, or subjects having a condition or disorder which can be treated by reducing caloric efficiency, nutrient availability, food intake, appetite, body weight or body weight gain, or increasing weight loss. Thus, Yoshinaga does not teach, expressly or inherently, each element recited in the claims, and the 102(b) rejection is improper.

Nor is the claimed invention rendered obvious by the Yoshinaga reference. (Although the examiner has made no formal 103(a) rejection based on this reference in the Office Action of November 23, 2006, during the interview, the Examiner stated that he may use the Yoshinaga reference to make such a rejection.) A 103(a) rejection is not proper. Firstly, the Examiner has not met his burden in establishing a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be

met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). (See M.P.E.P. §706.02(j)).The Yoshinaga reference does not teach or suggest all the elements of the claimed invention, at least for the reasons stated above. The claimed invention is also not inherent in the teaching of Yoshinaga. It cannot be assumed that the inhibition of pancreatic exocrine and gastric acid secretion in dogs of Yoshinaga are inherent or necessarily linked to the claimed effects of PYY agonist analogs such as reducing food intake, caloric efficiency, nutrient availability or appetite. Further, one of ordinary skill in the art would not have been motivated to modify the report of Yoshinaga to arrive at Applicants' invention with a reasonable expectation of success.

Although the Examiner has not met his burden in establishing *prima facie* obviousness, and the Office has never produced evidence sufficient to shift the burden to Applicants, solely to expedite prosecution and to illustrate that the Examiner is incorrect in his assumption that the parameters measured in Yoshinaga are necessarily and always linked to reduction of food intake, appetite, caloric efficiency or nutrient availability, Applicants submit the following references. These three papers illustrate a dissociation between gastric acid secretion and food intake for the hormones secretin and CKK. 1) Jin, *et al.*, (*Am. J. Physiol.* (1994) 267(4 Pt 1):G702-8) reports that secretin inhibits gastric acid secretion and gastric emptying in dogs. 2) Conover, *et al.*, (*Am. J. Physiol.* (1989) 256(1 Pt 2):R56-62) reports that secretin potently inhibits gastric emptying but has no effect on food intake. This reference also reports that gastric emptying is not sufficient to explain the satiety effect of CCK. 3) Muurahainen, et al., (*Physiol. Behav.* (1988) 44(4-5):645-9) reports that gastric emptying does not mediate the effects of CCK on food intake.

Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 1, 8, 33-42, 47-50 and 52-62 were rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Okada, et al., (The Endocrine Society 75th Annual Meeting Program & Abstract, page 180, Abstract 520B, 1993). Applicants respectfully traverse the rejection, because Okada does not teach, expressly or inherently, each element recited in the claims.

Okada teaches a reduction in food intake upon administration of full-length PYY (PYY[1-36]) to normal rats fed a diet containing 56% fat. Okada does not teach or suggest that administration of PYY[1-36] has any effect on intake of any food other than a diet containing 56% fat. Therefore, at most, Okada teaches that PYY may influence the state of satiation of a rat upon being fed this high-fat meal. Okada does not teach every element of the claimed invention. For example, Okada does not teach the claimed subject populations, does not teach reducing caloric efficiency, nutrient availability or appetite for any other kind of diet, and does not teach PYY[3-36] or any other N-terminally truncated PYY agonist analogs. The amended claims require a PYY agonist analog that is a "peptide which does not comprise YP as its first two consecutive N-terminal amino acids, and wherein the PYY agonist analog elicits a pharmacological effect at a Y2, Y5 or Y7 receptor greater than that of PYY[1-36] at a Y1 receptor."

Because the examiner has not established that each element required by the claims is expressly or inherently anticipated by Okada, Applicants respectfully submit that the 102(b) rejection is improper. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

Rejections Under 35 U.S.C. § 103(a)

Claims 44, 46 and 63 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Okada. The Examiner alleges that the lowest dosage administered to Okada's rats reads on the dose range of PYY claimed in the instant invention, and that "it would have been obvious to one having ordinary skill in the art at the time the invention was made to administer PYY to a human subject to reduce appetite or food intake with a reasonable expectation of success in view of the teachings of Okada et al. on the rats." (Office Action 23 November 2005, page 17). Applicants disagree and respectfully request reconsideration and withdrawal of these rejections.

The teachings of Okada fail to satisfy the criteria necessary for rendering the claimed invention obvious. The reference or teachings must teach or suggest each and every limitation of the claimed invention. Okada teaches that administration of PYY to normal rats is associated with a reduction of high-fat food intake. Okada does not teach the claimed subject populations. Okada is silent with regard to the effects of PYY administration on reduction of caloric efficiency, nutrient availability, body weight, weight gain, or increasing weight loss, or reducing appetite for anything but a diet containing 56% fat.

Moreover, Okada teaches the use of full length PYY, and does not teach PYY[3-36] or any other PYY agonist analogs. The amended claims further require a PYY agonist analog that is a "peptide which does not comprise YP as its first two consecutive N-terminal amino acids, and wherein the PYY agonist analog elicits a pharmacological effect at a Y2, Y5 or Y7 receptor greater than that of PYY[1-36] at a Y1 receptor." It should be noted that, at the time of filing, PYY[1-36] was known to have pharmacological effects at the Y1 receptor (see Table 1 of the application), and was reported to be a potent vasoconstrictor. The Y1 receptors located on vascular smooth muscle cells are believed to mediate this pressor effect (see Gehlert, D. R., Proc. Soc. Exp. Biol. Med. 218:7-22 (1998), pages 14, left column, through page 15, left column; and US Patent 5,696,093, column 2). The claimed PYY agonist analogs have the unexpected advantage of eliciting a pharmacological effect at a Y2, Y5 or Y7 receptor greater than that of PYY[1-36] at a Y1 receptor, avoiding the pressor effect. It would not have been obvious to one of ordinary skill in the art that a truncation removing the first two amino acids of the PYY[1-36] molecule used by Okada, would result in a PYY agonist analog that preserves the pharmacological effect on reducing food intake, but abolishes Y1 receptor binding and the effect on blood pressure. Prior to Applicants' disclosure, one of skill in the art would not have had a reasonable expectation of success in applying the teachings of Okada to the methods of the claimed invention.

The Examiner has failed to make a *prima facie* case that Okada renders the invention obvious because not all the elements of the claimed invention are found within the teachings of Okada, the reference provides no motivation to modify those teachings,

and one of ordinary skill in the art would not have a reasonable expectation of success. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Conclusion

In light of the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of all objections and rejections set forth in the Office Action of 23 November 2005. Further, Applicants believe all claims presently under consideration to be in a condition for allowance and request issuance of a Notice of Allowance at the Examiner's earliest convenience.

Should the Examiner have any remaining questions regarding the subject invention or its patentability, Applicants encourage the Examiner to contact the undersigned to discuss any issues remaining.

Respectfully submitted,

May 17, 2006

Susan J. Myers Fitch, Ph.D.
Registration No. 55,477

AMYLIN PHARMACEUTICALS, INC.
9360 Towne Centre Drive
San Diego, CA 92121
Telephone: (858) 552-2200
Fax: (858) 552-1936